Regulatory Education for Industry (REdI):
GENERIC DRUGS FORUM

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Inspections
Case Histories & Current Topics

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Agenda

- OPQ Office -Integrated Review process
- Facility Review Process- PAI Inspections
- Pre- Approval Inspections/Withholds
- Data/ Application Integrity - Examples
- Case Histories- Regulatory Actions
- Surveillance Inspection
- Q & A

OPQ: One Quality Voice- Value Statements

- **Put patients first by balancing risk and availability**
- ***Have one quality voice by integrating review and inspection across product lifecycle***
- **Safeguard clinical performance by establishing scientifically sound quality standards**
- **Maximize focus and efficiency by applying risk-based approaches**
- **Strengthen the effectiveness of lifecycle quality evaluations by using team based processes**

Facility Requirements for Applications

The FD&C Act states that FDA cannot approve an application to market if:

"the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging of such drug are inadequate to preserve its identity, strength, quality, and purity" § 505(d)(3)

- **How does FDA accomplish this?**

Application- Facility Reviews

- Before approval, FDA reviews the sites that will manufacture the drug
- Determines if an inspection is required
- The sites include:
  - Finished Dosage Form (FDF)
  - Active Pharmaceutical Ingredient (API)
  - Packaging
  - Testing Laboratories
  - Some complex intermediates
- Volume of Applications- ANDA (~1000/Y), NDA (~ 125/Y) and Supplements(~1000/Y)

How do we do Site Reviews?

- **All sites in an application is reviewed**
- **Reviews : API, Tableting, Liquid, Sterile, Complex technologies, DMF reviews**
- **FDA uses a risk-based tiered system**

  The "2-3-4" rule:

  - **2 years for FDF site**
  - **3 years for API or lab test site**
  - **4 years for packaging only site**

  What if "2-3-4" Rule Not Met?

  - **FDA will conduct a GMP surveillance inspection**

When to Perform a PAI--*Special Conditions*:

1. **Facility - First time for an application**
2. **First ANDA for an approved drug**
3. **Finished product contains a New Molecular Entity (NME)**
4. **Finished product content assay has a narrow range**
5. ***Substantially different manufacturing process* or dosage form**
6. **API derivation is high risk or intended use has significantly changed**

PAI Objectives

Data & Application Integrity

All records are accurate representations of:

- **Tests performed and test results**
- **Actual manufacturing & quality control**
- **Assay validations and " OOS investigations"**
- **Unexplainable discrepancies between:**
  - **Data submitted to the FDA**
  - **Data found during inspection**

Data that lacks integrity is….

- Unreliable
  - Omission of significant data from the submission that is determined to be material to the review process
  - Data that is not submitted, but should have been
- Inaccurate
  - e.g., first data failed specs, retest data passes specs, lab investigations are inadequate or non-existent, but retest data is submitted to the application
- Re-running samples (e.g. HPLC /GC)
- Backdating/Fabricating data/Discarding data
- No raw data to support final results
- Fabricating data/Discarding data
- Copying existing data as new data

Application Integrity Policy

- An “administrative action” to address submission of unreliable data
- Once AIP is invoked, FDA suspends review of the application/s until the provisions of the AIP are met
- Intended to assure the accuracy and reliability of data submitted to FDA for scientific review and approval
- Revoking AIP – What does it mean?

Overall Recommendations

- If *any one* site is unacceptable:
  - If any enforcement action pending or has occurred; or
  - If recent surveillance inspections show problems with currently marketed product; or
  - If PAI specific issues are found
    - more on next slide
- Then the application is <u>NOT</u> approvable for the sites identified

Pre Approval Inspection
Some Common Reasons to Withhold

1. **Significant data integrity problems;**

2. **Serious CGMP concerns with the manufacture of a bio-batch or demonstration batch;**

3. **Significant differences between the process used for pivotal clinical batches and the NDA submission batch;**

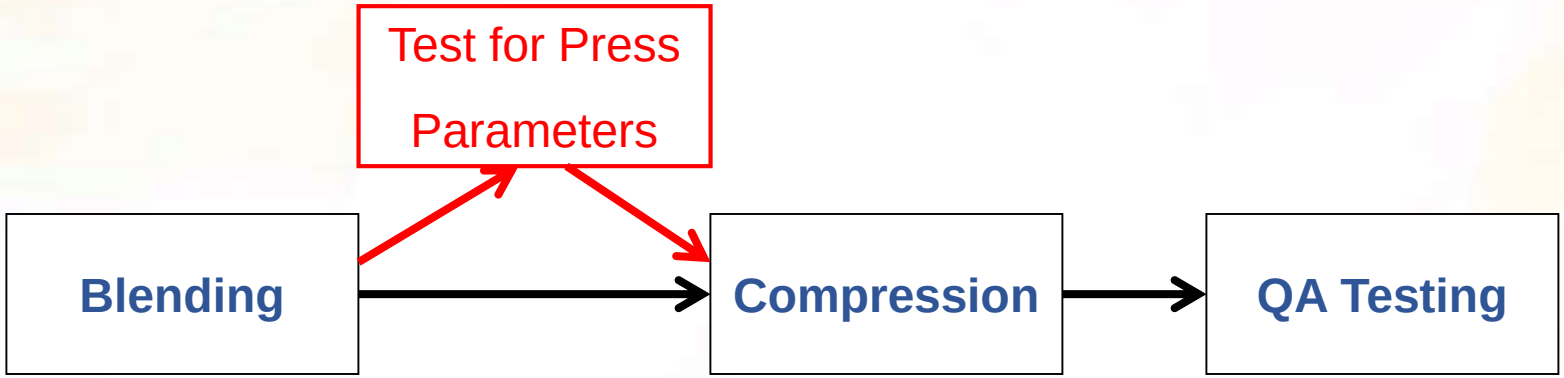
4. **Lack of complete manufacturing and control instructions in the master production record;**

5. **Process validation batch failures;**

Case 1: Process Validation

Background:

- **Firm markets an extended release tablet.**
- **First, the firm manufactures extended release "beads."**
- **The "beads" are blended and compressed with excipients.**
- **Operations had to pre-compress blend samples in the lab to determine operating parameters for the tablet press.**
- **Different blends would require different settings, and the firm had no idea why.**



Case 1: Process Validation

What Happened next:

- **During a routine FDA inspection, investigators saw the pre-compression practice.**
- **Investigators also found inadequate release testing, especially in light of known process problems.**
- **Warning Letter issued for lack of process validation.**
- **Full market withdrawal.**

Case 2: Resting on Your Laurels

Background:

- **Firm manufactures multiple transdermal patch products, and has been doing so for many years.**
- **Firm developed a new drug, utilizing the same adhesion matrix as it did for others.**
- **1st year on the market – received ~5000 complaints regarding efficacy, and difficulty to use (peel force problem).**
- **Complaints indicated that up to 25% of the drug was sticking to the liner, thus not being in the patch when applied to the skin.**

Case 2: Resting on Your Laurels

What Happened:

- **Firm investigation pointed to a specific drug/adhesive interaction problem**
- **Firm argued that since there were no specifications regarding peel force in their application, a recall wasn't warranted, and it could continue to distribute**
- **After further conversations with FDA, the firm initiated a full recall**
- **FDA issued a Warning Letter citing lack of specifications, as well as a failure to assure proper strength**
- **There is now a peel force specification in place**

Case 3: Turning a Blind Eye

- Firm manufactures an injectable drug
- FDA investigation of multiple adverse events pointed to a product made by the firm
- FDA inspected the firm
- Complaints reviewed by the firm indicated the presence of endotoxin in the finished product
- Firm had not identified a root cause
- Firm started to test for endotoxin in-process, prior to terminal sterilization, “for information only”
- Firm had found in-process results that were OOS, but finished product tested within specification

Case 3: Turning a Blind Eye

What Happened Next:

- **FDA issued a Warning Letter**
- **After discussions with FDA, firm recalled the product**
- **As a corrective action, the firm worked with the agency to develop a work plan**
- **Source detected in raw material**

Takeaway:

- **"Quality is built into pharmaceutical products through a comprehensive understanding of design and manufacturing process"**

Surveillance - Oversight Strategy

- Globally across all sites
- Assess the “state of quality” across a very diverse population of facilities
- For a given site:
  - Assess state of quality across product lines and systems
- Is a function of the reliability and accessibility of relevant quality data

Surveillance Inspection- Improving Efficiency

- **Information provided to investigator:**
  - **Products and Process**
  - **Facility Factors- Establishment type, Inspection history , size of facility**
  - **Time since last inspection**

- **Analysis across Product lines and key systems at site**

- **Quality metrics, reported by product, could provide valuable input?**

- **How to maximize the use of information collected on previous inspections?**

What is the Emerging Technology Team?

- **Small cross-functional team from all relevant CDER programs**

  Vision: *Encourage and support the adoption of innovative technology*

- **Serve as advocates for innovative technology while balancing risk vs. benefit**
- **Identify and evaluate roadblocks relating to existing guidance, policy, or practice**
- **Early applicant engagement with the ETT is recommended**
- **Contact us: CDER-ETT@fda.hhs.gov**

Summary

- **“One Quality Voice” with integrated review and inspections process will help in focusing and streamlining our inspection process**
- **Firms require additional measures and increased self audits to identify data integrity issues**
- **“Quality is built into pharmaceutical products through a comprehensive understanding of:**

  Product design, manufacturing, engineering, material science and QA to ensure acceptable and reproducible product quality….”
- **Risk based surveillance inspection will help to prioritize inventory of facilities**

Resources

For more on PAI Inspections…

Compliance Program Guidance Manual

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf

Questions and Answers

Current GMP Manufacturing Practices

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm

Questions?

Evaluation: surveymonkey.com/s/GDF-D1S6